

### **REMARKS**

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

#### Request for Continued Examination

Applicants hereby request continued examination of the present application under 37 C.F.R. §1.114.

#### Claims Amendments:

Claim 1 has been amended to recite an effective amount of "the virus" instead of an effective amount of "virus" to correct a typographical error. Moreover, claim 1 is also amended to recite that the virus is capable of selectively "replicating in and" killing tumor cells to describe the virus more completely. Support for this recitation can be found, for example, at page 13, lines 14-19.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants wish to point out that the amendments presented herein are made in the interest of expediting prosecution of the present application. Thus, Applicants submit that none of the claims now presented or previously presented are anticipated by or rendered obvious over the prior art.

#### Rejection Under 35 U.S.C. §102:

The rejection of claims 1-8 and 11-16 under 35 U.S.C. §102 as allegedly being anticipated by Barber et al. (U.S. Patent No. 5,662,896) is obviated in part and traversed in part as set forth below.

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall*, 198 USPQ 344 (CCPA 1978).

Claim 1, as amended, is directed to a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration selected from the group consisting of:

- (a) delivering on the same day a composition comprising the virus to multiple sites inside the solid tumor; and
- (b) delivering directly into the tumor a composition comprising the virus, wherein the volume of the composition is between about 10% to about 100% of the volume of the tumor.

Barber et al. relate to methods for inhibiting tumor growth using recombinant viral vectors. The vector encodes an anti-tumor agent, such as an immune activator or a proliferation inhibitor. Expression of the anti-tumor agent leads to either (1) direct inhibition of tumor cell division, or (2) immune cell mediated tumor cell lysis, or both, resulting in reduced tumor growth (see, for example, column 5, lines 27-36 of Barber et al.). Therefore, the viral vector is used as a vehicle to express the anti-tumor agent. In the claimed invention, however, the virus itself lyses tumor cells by replicating in and killing tumor cells. Moreover, claim 1 requires that the virus be capable of selectively replicating in tumor cells but not normal cells. Since Barber et al. do not teach the use of any virus that is capable of selectively replicating in tumor cells, the reference does not teach each and every element of claim 1.

Furthermore, Barber et al. do not teach multiple injections in the same tumor mass on the same day. The Office Action states that Barber et al. teach "For example, within one embodiment a small metastatic lesion may be located and the [retroviral] vector injected several times in several different locations within the body of the tumor". The Office Action thus concludes that Barber et al. teach administration of at least 3 injections on the

same day. However, nowhere do Barber et al. indicate that the injections are made on the same day.

In addition, Barber et al. do not teach the delivery of a viral composition to a tumor wherein the volume of the composition is between about 10% to about 100% of the volume of the tumor. The Office Action states that Barber et al. teach the administration of about one tenth to two-tenths of a milliliter of a viral vector into tumors that are about 1-4 mm<sup>3</sup> in volume, which the Office Action considers to be an administration of about 100% of the tumor volume. Applicants disagree. One milliliter corresponds to one cm<sup>3</sup>, which equals to 1000 mm<sup>3</sup>. Therefore, one tenth to two-tenths of a milliliter corresponds to 100 to 200 mm<sup>3</sup>. Even with the word "about", 100 to 200 mm<sup>3</sup> can not be considered about 100% of 1-4 mm<sup>3</sup>.

Thus, Barber et al. do not teach each and every element of claim 1. Claims 2-8 and 11-16 all depend from claim 1, and therefore contain all the elements of claim 1. Consequently, Barber et al. also do not teach each and every element of claims 2-8 and 11-16. Therefore, the requirement under 35 U.S.C. §102 is not met, and withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §103:

A. The rejection of claims 2-6 and 17-21 under 35 U.S.C. §103(a) as allegedly being unpatentable over Barber et al. (U.S. Patent No. 5,662,896) in view of Lee et al. (WO 99/08692) is respectfully traversed for the following reasons.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.*

Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

Claims 2-6 and 17-21 depend directly or indirectly from claim 1, further reciting that the virus is reovirus. Therefore, all these claims relate to methods for delivering reovirus to a solid tumor to reduce growth of the tumor, comprising:

- (a) delivering on the same day a composition comprising the reovirus to multiple sites inside the solid tumor; or
- (b) delivering directly into the tumor a composition comprising the reovirus, wherein the volume of the composition is between about 10% to about 100% of the volume of the tumor.

As elaborated above, Barber et al. do not teach or suggest the delivery of a virus to multiple sites in the tumor mass on the same day, or the delivery of a composition in a volume that is about 10%-100% of the volume of the tumor. Lee et al. teach the use of reovirus in reducing tumor growth, but do not specify that delivery of a virus to multiple sites in the tumor mass on the same day, or delivery of a composition in a volume that is about 10%-100% of the volume of the tumor, are advantageous. Since neither reference teaches or suggests these required elements of the rejected claims, nor does combination of the references. Accordingly, this rejection does not satisfy the criterion that the prior art reference or the combination of references must teach or suggest all the claim limitations. Since all three criteria are required under 35 U.S.C. §103, we do not need to discuss if the other two criteria are met.

Therefore, this rejection does not satisfy all the required criteria under 35 U.S.C. §103, and its withdrawal is respectfully requested.

2. The rejection of claims 9-10 under 35 U.S.C. §103(a) as allegedly being unpatentable over Barber et al. (U.S. Patent No. 5,662,896) is respectfully traversed as set forth below.

Claims 9 and 10 relate to methods for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of the virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells. Claim 9 recites that the virus is delivered on the same day to at least 5 sites inside the tumor mass, and claim 10 requires that the virus is delivered to one site per about 0.25 cubic centimeter of the tumor.

The Office Action states that Barber et al. teach the injection of a retroviral vector several times in several locations within the body of the tumor, but not administration of at least 5 sites inside the tumor mass or at least one site per 0.25 cubic centimeters of the tumor. However, citing *in re Aller*, 105 USPQ 233 (CCPA 1955), the Office Action alleges that it would have been *prima facie* obvious to perform routine optimization.

As discussed in the reply filed May 28, 2002, a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum of said variable might be characterized as routine experimentation. *In re Antonie*, 195 USPQ 6 (CCPA 1977). MPEP §2144.05, II.B. In *in re Antonie*, the invention was a water treatment device with a tank in which contactors continuously rotate. The primary prior art reference showed the device's basic structure but was silent regarding quantitative design parameters other than to give data on a single example. The claimed device has a ratio of tank volume to contactor area of at least about 0.12 gallon/ft<sup>2</sup>, and the Patent Office rejected the claims on the ground of obviousness in view of the prior art reference. The Court of Customs and Patent Appeals reversed, noting:

"In *In re Aller*, 220 F.2d 454, 42 CCPA 824, 105 USPQ 233 (1955), the court set out the rule that the discovery of an optimum value of a variable in a known process is normally obvious. We have found exceptions to this rule... (omitted) This case, in which the parameter optimized was not recognized to be a result-effective variable, is another exception".

*In re Antonie*, 195 USPQ at 8-9.

Here, Barber et al. do not recognize that the number of injections in the same tumor mass on the same day, let alone an injection per about 0.25 cubic centimeter of the tumor, is a result-effective variable which can be used to optimize the result. Therefore, under *in re Antonie*, the present case constitute an exception to the *in re Aller* rule.

Accordingly, the claimed invention is not obvious in view of Barber et al., and withdrawal of the rejection is respectfully requested.


Conclusions:

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 622-2340.

Respectfully submitted,

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**Attachment to Amendment and Reply dated December 11, 2002**

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Claims

1. (twice amended) A method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of the virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration selected from the group consisting of:
  - (a) delivering on the same day a composition comprising the virus to multiple sites inside the solid tumor; and
  - (b) delivering directly into the tumor a composition comprising the virus, wherein the volume of the composition is between about 10% to about 100% of the volume of the tumor.